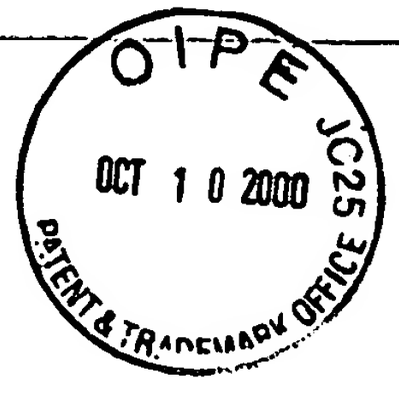
B7 sub C3

consisting of said first modification in said gene of interest and said second modification in said gene of interest.



REMARKS

Status of the Application

Claims 1-34 are pending in the present application.

Claims 9, 23, 29, and 32 have been cancelled, and Claims 1, 3, 15, 17, 31, and 34 have been amended to expedite Applicants' business interests, without acquiescing to any of the Examiner's arguments, while expressly reserving the right to prosecute the un-amended (or similar) claims in another application.

In particular, Claims 1 and 15 have been amended to recite that the embryonic stem cells are derived from mouse.

Claims 3, 17, 31, and 34 have been amended to replace the term "organism" with the term "non-human animal" as suggested by the Examiner.

Claims 35 and 36 have been added to more clearly describe Applicants' invention. In particular, Claims 35 and 36 include the same limitations as those of the herein-amended Claims 3 and 17, except that Claims 35 and 36 are in an independent form. Since the Examiner indicated that Claims 3 and 17 are "free of the cited prior art of record,"[1] and since new Claims 35 and 36 include each of the limitations of Claims 3 and 17, it follows that new Claims 35 and 36 are also free of the cited prior art.

Applicants' amendments do not introduce new matter.

Applicants note the Examiner's withdrawal of the following rejections which were advanced in the prior Office Action mailed on January 18, 2000, and which were not reiterated in the instant Office Action: (a) rejection of Claims 3, 13, 17 and 27 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement; (b) rejection of Claims 3 and 17 under 35 U.S.C. §112, second paragraph for alleged indefiniteness; (c) rejection of Claims 1, 2, 4, 6, 8, 9-11, and 13 under 35 U.S.C. §102(a) for alleged anticipation by Cohen-Tannoudji *et al.*; (d) rejection of Claims 1-7, 9-11, 14-21, 23-25 and 28 under 35 U.S.C. §102(b) for alleged anticipation by Marker *et al.*; (e) rejection of Claims 1, 9, 12, 15, 23, and 26 under 35

[1] Office Action, page 7, first full paragraph.

U.S.C. §103(a) for alleged obviousness over Marker *et al.* and Schulte-Merker *et al.*; and (f) rejection of Claims 1, 6, 8, 15, 20, and 22 under 35 U.S.C. §103(a) for alleged obviousness over Marker *et al.* and Slamenova *et al.*

Claims 30 and 33 are allowed.[2]

The Examiner advanced the following objections and rejections to Claims 1-29, 31, 32, and 34:

1. The petition to correct inventorship has been objected to under 37 C.F.R. §3.73(b);

2. Claims 3, 9, 17, 23, 31, and 34 were objected to because of informalities relating to claim election;

3. Claims 1-12, 14-26, 28, 29, 31, 32, and 34 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement; and

4. Claims 1, 2, 4, 6, 7, 9-11, 13-16, 18, 20, 21, 23-25, 27, and 28 continue to be rejected under 35 U.S.C. §102(a) as being anticipated by Thomas *et al.*

Applicants believe that the present amendments and the following remarks overcome the Examiner's objections and rejections of the claims. These remarks are presented in the same order as they appear above.

1. Objection To Correction Of Inventorship Under 37 C.F.R. §3.73(b)

The petition to correct inventorship has been objected to under 37 C.F.R. §3.73(b).[3] Applicants hereby submit a "Certificate Under 37 C.F.R. §3.73(b) Establishing Right of Assignee To Take Action," including two "Notice of Recordation of Assignment Document" which show assignment by the inventors to the sole assignee, Case Western Reserve University. Applicants believe this showing overcomes the Examiner's objection.

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[2] Office Action, page 1, "Disposition of Claims;" and page 7, first full paragraph.

[3] Office Action, page 2.

2. **Objection To Claims 3, 9, 17, 23, 31, and 34 Relating To Election of Claims**

Claims 3, 9, 17, 23, 31, and 34 were objected to because of informalities relating claim election.[4] The objection rests on the Examiner's prior indication in the Office Action mailed on January 18, 2000 that claims which recite "cell" and "organism" are examined only as they pertain to cells and organisms from non-human animals.

Applicants have cancelled Claims 9 and 23, and amended Claims 3, 17, 31, and 34 to replace the term "organism" with the term "non-human animal" as suggested by the Examiner, thereby overcoming the objection to these claims.

3. **Rejection Of Claims 1-12, 14-26, 28, 29, 31, 32, and 34 Under 35 U.S.C. §112, First Paragraph (Non-Enablement)**

Claims 1-12, 14-26, 28, 29, 31, 32, and 34 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.[5] Applicants respectfully disagree.

The Examiner recognized that the specification is enabling for fertilized egg cells and 2-cell embryos from any animal, and for mouse embryonic stem cells.[6] The Examiner further recognized that mouse embryonic stem cells are enabled for giving rise to chimeric mice[7] which may contain the recited genetic modifications in either somatic cells alone, germline cells alone, or both somatic and germline cells.[8] Nonetheless, the Examiner continued to reject Claims 1-12, 14-26, 28, 29, 31, and 34 as being allegedly not enabled for embryonic stem cells which are not limited to those derived from mouse. Applicants' amendment of

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[4] Office Action, page 3, first two paragraphs.

[5] Office Action, page 4, first paragraph.

[6] Office Action, page 4, first and second paragraphs.

[7] Office Action, page 5 first paragraph.

[8] See Applicants "Amendment And Response Under 37 C.F.R. §1.111 To Office Action Mailed January 18, 2000" which was mailed to the Office on April 18, 2000.

independent Claims 1 and 15 (to recite that the embryonic stem cells are derived from mouse) overcomes the Examiner's rejection of Claims 1-12, 14-26, 28, 29, 31, and 34.[9]

The Examiner also has rejected Claim 32 on the ground that "Nowhere in the specification would one of skill in the art find guidance and/or direction for the use of . . . protocorm-like [body] or callus cells for the contribution to tissues of a chimeric animal."[10] In the first instance, the Examiner erroneously refers to protocorm-like body cells and callus cells as starting material to generate **animal** tissues or organisms, since these cells contribute to generation of **plant** tissues and whole plants. Second, the Examiner's rejection is mooted by cancellation of Claims 29 and 32.[11]

In view of the above, it is respectfully requested that the rejection of Claims 1-12, 14-26, 28, 29, 31, 32, and 34 under 35 U.S.C. §112, first paragraph, be withdrawn.

4. Rejection Of Claims 1, 2, 4, 6, 7, 9-11, 13-16, 18, 20, 21, 23-25, 27, and 28 Under 35 U.S.C. §102(a) Over Thomas *et al.*

Claims 1, 2, 4, 6, 7, 9-11, 13-16, 18, 20, 21, 23-25, 27, and 28 continue to be rejected under 35 U.S.C. §102(a) as being anticipated by Thomas *et al.*[12] The Examiner found that the *In re Katz* Declaration executed by co-inventor Dr. Magnuson was insufficient to overcome anticipation under §102(a) by Thomas *et al.* since the inventive entity (*i.e.*, Richard P. Woychik, Terry R. Magnuson, Ellis D. Avner, and James W. Thomas)[13] of the application

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[9] The claims have been amended to expedite Applicants' business interests, without acquiescing to any of the Examiner's arguments, while expressly reserving the right to prosecute the un-amended (or similar) claims in another application.

[10] Office Action, page 5, last sentence of first paragraph.

[11] The claims have been amended to expedite Applicants' business interests, without acquiescing to any of the Examiner's arguments, while expressly reserving the right to prosecute the un-amended (or similar) claims in another application.

[12] Office Action, page 6.

[13] This inventive entity assumes grant of Applicants' petition to add under 37 C.F.R. §1.48(a) James W. Thomas as a co-inventor. Applicants' petition was mailed to the Office on April 18, 2000.

differs from the "inventive entity" of Thomas *et al.*[14] Applicants respectfully disagree since Thomas *et al.* does not disclose all the limitations of the rejected claims.

> The law is clear that:
>
> "Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration."[15] Conversely, "absence from the reference of any claimed element negates anticipation."[16]

Thomas *et al.* does not disclose either providing a "chemical agent," or treating cells with the "chemical agent" as recited in steps a) and b), respectively, of each of the rejected claims. Thomas *et al.* discloses treating mouse embryonic stem cells with **X-rays or UV light**,[17] not with a **chemical agent**. Because a critical limitation of the claims is absent from Thomas *et al.*, this reference cannot form the basis of a rejection premised on anticipation. Accordingly, Applicants respectfully request that the rejection of Claims 1, 2, 4, 6, 7, 9-11, 13-16, 18, 20, 21, 23-25, 27, and 28 under 35 U.S.C. §102(a) be withdrawn.

Conclusion

All grounds of rejection and objection of the pending Office Action having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in

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[14] Office Action, page 6, last paragraph.

[15] *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301, adopted, 149 USPQ 640 (Ct. Cl. 1966).

[16] *Rowe v. Dror*, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997), citing *Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986).

[17] Thomas *et al.*, page 1115, second column, third paragraph.

the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (415) 705-8410.

Dated: October 10, 2000

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Registration No. 38,230

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APPENDIX I

PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

The following is a list of the claims as they would appear following entry of this amendment.

1. (Twice amended) A method of producing a modification in a gene of interest contained in a cell, comprising:

a) providing:

i) an *in vitro* culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from fertilized egg cells, cells of 2-cell embryos, and mouse embryonic stem cells;

ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells and at least one modification in one or more additional genes;

b) treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest and cells having a modified gene of interest; and

c) isolating said cells having a modified gene of interest.

2. The method of Claim 1, further comprising step d) comparing the nucleotide sequence of said gene of interest in said cells having a modified gene of interest with the nucleotide sequence of said gene of interest in said cells having an unmodified gene of interest.

3. (Twice amended) The method of Claim 1, further comprising d) placing at least one of said cells having a modified gene of interest into an environment under conditions so as to generate a non-human animal comprising said modification in said gene of interest.

4. The method of Claim 2, further comprising prior to step d) amplifying said modified gene of interest to produce an amplified modified gene of interest.

5. The method of Claim 4, further comprising prior to step d) sequencing said amplified modified gene of interest.

6. The method of Claim 1, wherein said modification is selected from the group consisting of mutation, mismatch, and strand break.

7. The method of Claim 6, wherein said mutation is selected from the group consisting of deletion, insertion and substitution.

8. The method of Claim 6, wherein said strand break is selected from the group consisting of single-strand break and double-strand break.

10. The method of Claim 9, wherein said non-human animal is a mammal.

11. The method of Claim 10, wherein said mammal is a mouse.

12. The method of Claim 9, wherein said non-human animal is zebrafish.

13. (Once amended) The method of Claim 1, wherein said embryonic cell is a mouse embryonic stem cell.

14. (Once amended) The method of Claim 1, wherein said agent is selected from the group consisting of *N*-ethyl-*N*-nitrosurea, methylnitrosourea, procarbazine hydrochloride, triethylene melamine, acrylamide monomer, chlorambucil, melphalan, cyclophosphamide, diethyl sulfate, ethyl methane sulfonate, methyl methane sulfonate, 6-mercaptopurine, mitomycin-C, procarbazine, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, $^{3}H_2O$, and urethane.

15. (Twice amended) A method of producing an allelic series of modifications in a gene of interest contained in a cell, comprising:

a) providing:

i) an *in vitro* culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from fertilized egg cells, cells of 2-cell embryos, and mouse embryonic stem cells;

ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells;

b) treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest, cells having a first modification in said gene of interest, and cells having a second modification in said gene of interest; and

c) isolating said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest, thereby producing an allelic series of modifications in said gene of interest in the isolated cells.

16. The method of Claim 15, further comprising step d) comparing the nucleotide sequence of said gene of interest in said cells having an unmodified gene of interest with the nucleotide sequence of said gene of interest in cells selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest.

17. (Twice amended) The method of Claim 15, further comprising d) placing at least one cell selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest into an environment under conditions so as to generate a non-human animal comprising a modification selected from the group consisting of said first modification in said gene of interest and said second modification in said gene of interest.

18. The method of Claim 16, further comprising prior to step d) amplifying said gene of interest selected from the group consisting of said gene of interest having said first

modification and said gene of interest having said second modification to produce amplified modified gene of interest selected from the group consisting of amplified gene of interest having said first modification and amplified gene of interest having said second modification.

19. The method of Claim 18, further comprising prior to step d) sequencing said amplified modified gene of interest.

20. The method of Claim 15, wherein said first modification and said second modification are selected from the group consisting of mutation, mismatch, and strand break.

21. The method of Claim 20, wherein said mutation is selected from the group consisting of deletion, insertion and substitution.

22. The method of Claim 20, wherein said strand break is selected from the group consisting of single-strand break and double-strand break.

24. The method of Claim 23, wherein said non-human animal is a mammal.

25. The method of Claim 24, wherein said mammal is a mouse.

26. The method of Claim 23, wherein said non-human animal is zebrafish.

27. (Once amended) The method of Claim 15, wherein said embryonic cell is a mouse embryonic stem cell.

28. (Once amended) The method of Claim 15, wherein said agent is selected from the group consisting of *N*-ethyl-*N*-nitrosurea, methylnitrosourea, procarbazine hydrochloride, triethylene melamine, acrylamide monomer, chlorambucil, melphalan, cyclophosphamide, diethyl sulfate, ethyl methane sulfonate, methyl methane sulfonate, 6-mercaptopurine, mitomycin-C, procarbazine, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, $^{3}H_2O$, and urethane.

30. A method of producing a modification in a gene of interest contained in a mouse cell, comprising:

a) providing:

i) an *in vitro* culture of isolated mouse embryonic stem cells containing a gene of interest;

ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said mouse embryonic stem cells and at least one modification in one or more additional genes;

b) treating said mouse embryonic stem cells with said agent under conditions such that a mixture of embryonic stem cells is produced, said mixture of embryonic stem cells comprising cells having an unmodified gene of interest and cells having a modified gene of interest;

c) isolating said cells having a modified gene of interest;

d) comparing the nucleotide sequence of said gene of interest in said cells having a modified gene of interest with the nucleotide sequence of said gene of interest in said cells having an unmodified gene of interest; and

e) manipulating said cells having a modified gene of interest to generate an organism comprising said modification in said gene of interest, wherein said manipulating comprises:

i) introducing said cells having said modified gene of interest into a mouse embryo to produce a treated embryo;

ii) introducing said treated embryo into a pseudopregnant mouse; and

iii) permitting said pseudopregnant mouse to deliver at least one offspring comprising said modified gene of interest.

31. (Once amended) The method of Claim 3, wherein said non-human animal is chimeric.

33. A method of producing an allelic series of modifications in a gene of interest contained in a mouse cell, comprising:

a) providing:

i) an *in vitro* culture of mouse embryonic stem cells;

ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said mouse embryonic stem cells;

b) treating said mouse embryonic stem cells with said agent under conditions such that a mixture of embryonic stem cells is produced, said mixture of embryonic stem cells comprising cells having an unmodified gene of interest, cells having a first modification in said gene of interest, and cells having a second modification in said gene of interest;

c) isolating said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest, thereby producing an allelic series of modifications in said gene of interest in the isolated cells;

d) comparing the nucleotide sequence of said gene of interest in said cells having an unmodified gene of interest with the nucleotide sequence of said gene of interest in cells selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest; and

e) manipulating cells selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest to generate an organism comprising a modification selected from the group consisting of said first modification in said gene of interest and said second modification in said gene of interest, wherein said manipulating comprises:

i) introducing said cells having said first modification in said gene of interest and said cells having said second modification of said gene of interest into a mouse embryo to produce a treated embryo;

ii) introducing said treated embryo into a pseudopregnant mouse; and

iii) permitting said pseudopregnant mouse to deliver at least one offspring comprising said first modification in said gene of interest or said second modification in said gene of interest.

34. (Once amended) The method of Claim 17, wherein said non-human animal is chimeric.

35. (New) A method of producing a modification in a gene of interest contained in a cell, comprising:

a) providing:

i) an *in vitro* culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from fertilized egg cells, cells of 2-cell embryos, and mouse embryonic stem cells;

ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells and at least one modification in one or more additional genes;

b) treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest and cells having a modified gene of interest;

c) isolating said cells having a modified gene of interest; and

d) placing at least one of said cells having a modified gene of interest into an environment under conditions so as to generate a non-human animal comprising said modification in said gene of interest.

36. (New) A method of producing an allelic series of modifications in a gene of interest contained in a cell, comprising:

a) providing:

i) an *in vitro* culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from fertilized egg cells, cells of 2-cell embryos, and mouse embryonic stem cells;

ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells;

b) treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising

cells having an unmodified gene of interest, cells having a first modification in said gene of interest, and cells having a second modification in said gene of interest;

c) isolating said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest, thereby producing an allelic series of modifications in said gene of interest in the isolated cells; and

d) placing at least one cell selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest into an environment under conditions so as to generate a non-human animal comprising a modification selected from the group consisting of said first modification in said gene of interest and said second modification in said gene of interest.